REMARKS

Claim Amendements

Claims 1, 3, 5, 10-15, 18, 31-32, 40, 42, 95, 99, 147-148 and 150-153 are currently pending herein. Claims 1 and 3 have been amended herein. Claims 3, 5, 10-15, 18, 32, 40, 42, 95, 99, 147 and 150-153 have been withdrawn herein. Support for these amendments can be found throughout the specification and in the claims as previously filed. No new matter has been added.

Rejoinder

Applicants believe that Claims 1, 31 and 148 are in condition for allowance and, therefore, respectfully request that withdrawn Claims 3, 5, 10-15, 18, 32, 40, 42, 95, 99, 147 and 150-153 be rejoined.

Rejection of Claims 1, 31 and 148 Under requirements of 35 U.S.C. §103(a)

Claims 1 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Yu *et al.* (2000), in view of Kandimalla *et al.*, Liu *et al.*, Yu *et al.* (2002), Krieg and Wise *et al.*

Applicants thank the Examiner for the reminder that one cannot show nonobviousness by attacking the references individually where the rejections are based on a combination of the references. However, Applicants disagree that the response to the previous Office Action attacked the references individually. Rather, Applicants were pointing out the deficiency in the assertions made by the Office Action regarding the teachings of the cited references. Furthermore, Applicants would like to emphasize that teachings that are neither explicitly nor implicitly found within the reference cannot support a *prima facie* case of obviousness. Impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts from the prior art.

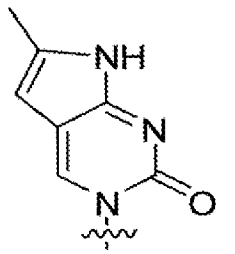
The instantly claimed invention is directed to an immunomer compound, comprising at least two oligonucleotides linked at their 3' ends, internucleoside linkages, functionalized nucleobase or sugar to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG, wherein R is a nucleotide having 2-oxo-7-deaza-8-methyl-purine as a

base and G is a nucleotide having a base selected from the group consisting of guanine, 2-amino-6-oxo-7-deazapurine, 2-amino-6-thiopurine, 6-oxo-purine or other non-natural purine. For the reasons discussed below, the Office Action fails to make its *prima facie* case of obviousness in view of the cited art.

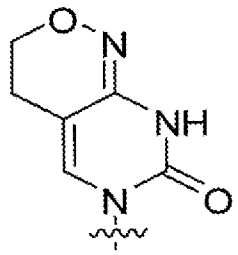
P-base does not represents a genus [that pyrrolo-dC is a specie thereof]

The Office Action continues to maintain that "P-base" represents a genus of which pyrrolo-dC is a species thereof. Applicants' rebuttal of this assertion has been rejected on the grounds that arguments of counsel cannot take place of the factually supported objective evidence in the record. However, in the instant rejection there is no **factually supported** evidence to support this assertion. Furthermore, at page 6 of the Office Action, there is reference to the "cytosine analogue P-base pyrrolocytosine". Applicants respectfully request clarification as to what exactly is the "cytosine analogue P-base pyrrolocytosine".

Pyrrolo-dC and P-base have the following structures:



Pyrrolo Base



P Base

As evidenced in the depiction above, P-base and pyrollo-dC are each distinct nucleoside base analogues. Thus, as consistently asserted by Applicants, there is no scientific rational for the Office Action's position that "P-base" represents a genus of which pyrrolo-dC is a species.

In an Office Action mailed from the USPTO on May 27, 2010, in related application 11/174,002, the Examiner states that Kandimalla (2001) uses the generic term "P-base" to describe the nucleotide species, and that Agrawal (WO 01/12804) discloses the **same compound**

to be recognized generically as "dP" (emphasis added). However, neither Kandimalla nor Agrawal use the term "generic" anywhere within the documents to describe P-base. In fact, as noted by the Office Action, both Kandimalla and Agrawal use the terms "P-base" and "dP" to describe the **same** nucleoside analogue. Furthermore, the use of the term "dP" by Agrawal is merely representative and is analogous to the use of "A", "T", "C" or "G" to describe adenosine, thymidine, cytidine or guanosine, respectively. One skilled in the art would not suggest that "A" or "adenosine" represent a genus of nucleosides (of which thymidine, cytidine or guanosine are species). As such, there is nothing in the objective evidence to support the position that "P-base" represents a genus.

Krieg does not teach modification of the CpG dinucleotide

According to the Office Action, Krieg discloses immunostimulatory oligonucleotides comprising C*pG motifs, whereby the cytosine (C*) is substituted for a cytosine derivative/analogue, i.e., a P-base." To support this assertion, the Office Action points to paragraph [0094] of Krieg.

Paragraph [0094] of Krieg states:

> "In particular formulas described herein a set of modified bases is defined. For instance the letter Y is used to refer to a nucleotide containing a cytosine or a modified cytosine. A modified cytosine as used herein is a naturally occurring or non-naturally occurring pyrimidine base analog of cytosine which can replace this base without impairing the immunostimulatory activity of the oligonucleotide. Modified cytosines include but are not limited to 5-substituted cytosines (e.g. 5-methyl-cytosine, 5-fluoro-cytosine, 5-chloro-cytosine, 5-bromo-cytosine, 5-iodo-cytosine, 5-hydroxy-cytosine, 5-hydroxymethyl-cytosine, 5-difluoromethyl-cytosine, and unsubstituted or substituted 5-alkynyl-cytosine), 6-substituted cytosines, N4-substituted cytosines (e.g. N4-ethyl-cytosine), 5-aza-cytosine, 2-mercapto-cytosine, isocytosine, pseudo-isocytosine, cytosine analogs with condensed ring systems (e.g. N,N'-propylene cytosine or phenoxazine), and uracil and its derivatives (e.g. 5-fluoro-uracil, 5-bromo-uracil, 5-bromovinyl-uracil, 4-thio-uracil, 5-hydroxy-uracil, 5-propynyl-uracil). Some of the preferred cytosines include 5-methyl-cytosine, 5-fluoro-cytosine, 5-hydroxy-cytosine, 5-hydroxymethyl-cytosine, and N4-ethyl-cytosine. In another embodiment of the invention, the cytosine base is substituted by a universal base (e.g. 3-nitropyrrole, P-base), an aromatic ring system (e.g. fluorobenzene or difluorobenzene) or a hydrogen atom (dSpacer). The letter Z is used to refer to guanine or a modified guanine base. A modified guanine as used herein is a naturally occurring or non-naturally occurring purine base analog of guanine which can replace this base without impairing the immunostimulatory activity of the oligonucleotide.

> Modified guanines include but are not limited to 7-deazaguanine, 7-deaza-7-substituted guanine (such as 7-deaza-7-(C2-C6)alkynylguanine), 7-deaza-8-substituted guanine, hypoxanthine, N2-substituted guanines (e.g. N2-methyl-guanine), 5-amino-3-methyl-3H,6H-thiazolo[4,5-d]pyrimidin- e-2,7-dione, 2,6-diaminopurine, 2-aminopurine, purine, indole, adenine, substituted adenines (e.g. N6-methyl-adenine, 8-oxo-adenine) 8-substituted guanine (e.g. 8-hydroxyguanine and 8-bromoguanine), and 6-thioguanine. In another embodiment of the invention, the guanine base is substituted by a universal base (e.g. 4-methyl-indole, 5-nitro-indole, and K-base), an aromatic ring system (e.g. benzimidazole or dichloro-benzimidazole, 1-methyl-1H-[1,2,4]triazole-3-carboxylic acid amide) or a hydrogen atom (dSpacer)."

This paragraph merely recites a laundry list of pyrimidine and purine analogues that theoretically can be incorporated somewhere into a CpG-containing oligonucleotide without impairing the immunostimulatory activity thereof. However, paragraph [0094] is silent with regards to the modification of the CpG motif.

The Office Action attempts to overcome this deficiency by stating that a "reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments." However, Applicants remind the PTO that the any reliance on a reference must be consistent with the teachings therein. The Office Actions interpretation of paragraph [0094] is completely inconsistent with paragraphs [0001]-[0093] and [0095]-[0338] of Krieg especially, for example, paragraphs [0074], [0075], [0080], [0085] and [0090] which state:

> [0074] The CpG motifs of the nucleic acids described herein are preferably unmethylated. An unmethylated CpG motif is an unmethylated cytosine-guanine dinucleotide sequence (i.e. an unmethylated 5' cytosine followed by 3' guanosine and linked by a phosphate bond). All the nucleic acid described herein are immunostimulatory. In some embodiments of the invention, the CpG motifs are methylated. A methylated CpG motif is a methylated cytosine-guanine dinucleotide sequence (i.e., a methylated 5' cytosine followed by a 3' guanosine and linked by a phosphate bond).;
>
> [0075] A CpG nucleic acid is a nucleic acid that comprises the formula
>
> 5' X.sub.1 X.sub.2**CG**X.sub.3 X.sub.4 3' (emphasis added)
>
> [0080] wherein X.sub.1X.sub.2, X.sub.3, and X.sub.4 are **nucleotides**. In preferred embodiments at least one of X.sub.3 and X.sub.4 are a G. In other embodiments both of X.sub.3 and X.sub.4 are a G. In yet other embodiments the preferred formula is 5' GGGNGGG 3', or 5' GGGNGGGNGGG 3' wherein N represents between 0 and 20 nucleotides. (emphasis added);

> [0085] For example, the oligonucleotides may comprise one or more modifications and wherein each modification is independently selected from:
>
> [0090] e) the replacement of a natural nucleoside base by a modified nucleoside base.

Therefore, [0074] and [0075] of Krieg clearly teach CpG-containing oligonucleotides having a wild-type (i.e., non-modified) CpG dinucleotide. The only place within the formula above that allows for any "theoretical" modification is in the sequence flanking the CG dinucleotide (Applicants describe any modification of the oligonucleotides of Krieg as theoretical because Krieg does not teach any oligonucleotide having any modification). Therefore, the replacement of a natural nucleoside in [0090] by a modified nucleoside base as described in [0094] is directed at the "nucleotides" of the CpG-containing oligonucleotide, i.e., X.sub.1X.sub.2, X.sub.3, and X.sub.4 of [0075] and [0080]. As such, Krieg **does not** teach an immunostimulatory oligonucleotides comprising C*pG motifs, whereby the cytosine (C*) is substituted for a cytosine derivative/analogue, i.e., a P-base.

Such a lack of teaching or suggestion is not irrelevant as one skilled in the art would understand that modifying the CpG can negatively affect the ability of a CpG-containing oligonucleotide to generate an immune response. In fact, as taught by Krieg in U.S. Patent 6,207,646 (hereinafter the '646 patent):

> "Mitogenic ODN sequences uniformly became **nonstimulatory** if the CpG dinucleotide was mutated (Table 1; compare ODN 1 to 1a; 3D to 3Dc; 3M to 3Ma; and 4 to 4a) or if the cytosine of the CpG dinucleotide was replaced by 5-methylcytosine (Table 1; ODN 1b,2b,3Dd, and 3Mb). Partial methylation of CpG motifs caused a partial loss of stimulatory effect (compare 2a to 2c, Table 1). In contrast, methylation of other cytosines did not reduce ODN activity (ODN 1c, 2d, 3De and 3Mc). These data confirmed that a CpG motif is the **essential** element present in ODN that activate B cells." (emphasis added)

The Office Action states that Applicants use of the Krieg's earlier '646 patent is not persuasive because it is not one of the references cited in the rejection and Krieg's later work (US 2004/0053880, which is relied upon in the rejection) describes immunostimulatory oligonucleotides in which the cytosine of the CpG motif is substituted for a P-base. Applicants disagree. As stated above, the '880 publication does not teach immunostimulatory oligonucleotides in which the cytosine of the CpG motif is substituted for a P-base. Additionally, Applicants would like to remind the Office that knowledge of the state of the art at

the time of invention is not limited to what is cited by the Examiner in a rejection. The teachings of the '646 patent in combination with the formula disclosed in paragraph [0075] of the '880 publication, clearly demonstrate that Krieg provides no teaching concerning the modification of the CpG motif.

Furthermore, as stated by Applicants in response to previous Office Actions, which are incorporated herein by reference, Kandimalla (2001) teaches that a YpG-containing oligonucleotide in which Y was deoxy-P-base nucleoside (referred to as "the first bicyclic non-natural cytosine" by the Office Action) showed **little or no immunostimulatory activity** (see page 809, column 2, lines 22-24)(emphasis added). This was clarified by Dr. Kandimalla's declaration which stated that such a modification rendered the compound inactive.

The Office Action attempts to overcome this deficiency by characterizing Kandimalla (2001) as demonstrating a 40% success of monocyclic cytosine analogues to provide the motivation with reasonable expectation of success for bicyclcic cytosine analogues. However, this overly simplified comparison by the PTO is unsupported by any evidence of record as 100% of the bicyclic analogues tested by Kandimalla (2001) did not work. Additionally, the Office Action fails to address whether there would be any functional differences between monocyclic and bicyclic analogues in the C position of the CG dinucleotide.

In a further attempt to support the rejection, and the relevance of Liu and Wise to the instantly claimed invention, the Office Action states that because Liu and Wise teach that pyrrolo-dC is highly fluorescent it would be useful for probing protein-nucleic acid interactions, and that one skilled in the art would have been motivated to modify the CpG dinucleotide with pyrollo-dC to study the structure-function relationships between CpG oligonucleotides and the protein receptor to which they bind.

Applicants respectfully disagree for several reasons. First, the basis for conclusion by the Office Action relies upon a misrepresentation of the teachings of Liu and Wise. As taught by Liu, pyrrolo-dC is a highly fluorescent cytidine analog with excitation and emission maxima far from those of DNA and protein. In other words, pyrrolo-dC itself is fluorescent. It does not become fluorescent upon interaction with DNA or a protein.

Furthermore, Liu teaches the incorporation of pyrrolo-dC into duplex DNA to study the formation of the elongation bubble which moves with the RNA polymerase active site. This

elongation bubble is the site of local melting of the duplex DNA into single-stranded DNA that allows for the transcriptional enzyme to transcribe the template DNA strand into RNA.

Liu goes on to state that pyrrolo-dC:

> like 2-aminopurine (Xu *et al.*, 1994; Xu & Nordlund, 2000), shows reduced fluorescence in duplex DNA relative to its fluorescence in single-stranded DNA. This quenching of fluorescence can be used to monitor local DNA melting.

(see pg. 467, lines 1-5).

In other words, Liu places pyrrolo-dC at specific positions in a non-template strand so that, as the RNA polymerase moves down the double-stranded DNA, the fluorescence of pyrrolo-dC can provide direct information on the local melting of the DNA. Therefore, it is this melting of the duplex DNA into single-stranded DNA that allows for the detection of the fluorescence of pyrrolo-dC and **not** any DNA-protein interaction.

The use of pyrrolo-dC as suggested in the Office Action may provide some information with regards to the uptake and internalization of a C*pG-containing oligonucleotide wherein C* is pyrrolo-dC; however there is no teaching within the cited references that would provide one skilled in the art with a reasonable expectation of success that such an oligonucleotide would bind to the receptor. This suggestion is hindsight reconstruction based on Applicants teachings that such a C*pG-containing oligonucleotide would even bind to the target protein receptor.

Moreover, as pointed out by the Examiner in the Office Action mailed from the USPTO on May 27, 2010, in related application 11/174,002, Zhu et al. already teaches a mechanism for studying the uptake and internalization of a CpG-containing oligonucleotide through the use of a fluorescent label. However, Zhu does not label the CpG dinucleotide and, therefore, doesn't support the Office Action's position that the teachings of Zhu would lead to such a modification.

Based on the teachings of Zhu, one skilled in the art would not be motivated to modify the C of a CpG dinucleotide with pyrrolo-dC when the skilled person could simply label the oligonucleotide as taught by Zhu (without modification to the CG dinucleotide). Furthermore, if one skilled in the art wanted to use pyrrolo-dC as the fluorescent marker there would be nothing preventing the incorporation of the pyrrolo-dC into the oligonucleotide in a position other than the CpG dinucleotide as taught by Zhu. This alternate incorporation would allow the use of pyrrolo-dC natural fluorescence and eliminate the possibility of inactivating the CpG

dinucleotide. As such, the conclusory statements by the Office Action that Liu would provide the motivation to modify the C of a CpG dinucleotide with pyrrolo-dC are not supported.

Applicants would like to remind the PTO that the claims are directed to an "immunostimulatory oligonucleotide". Any proposed combination of the cited art that fails to teach an oligonucleotide that generates an immune response, or at least provides a reasonable expectation of success thereof, does not render the claimed invention obvious.

Furthermore, none of Applicant's assertion has been changed by the Supreme Court's decision in KSR. The Federal Circuit has more recently addressed the application of KSR to a complex and unpredictable chemical case in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-7 (2007). The discussion in that case very well reconciles KSR with decades of the law of obviousness in complex chemical cases, so a portion of the decision is cited here.

> Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.
>
> We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon,* 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. In re Grabiak, 769 F.2d 729, 731-32 (Fed.Cir.1985).
>
> We elaborated on this requirement in the case of *In re Deuel,* 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.,* an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed.Cir.1992); *Dillon,* 919 F.2d 688; Grabiak, 769 F.2d 729; *In re Lalu,* 747 F.2d 703 (Fed.Cir.1984)).
>
> That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in KSR. While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court

> acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* **Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.** (emphasis added)

The ordinary artisan would not have a reasonable expectation of success that an oligonucleotide comprising the cytosine analogue pyrrolo-dC instead of cytosine in a CpG motif would be immunostimulatory for the reasons discussed above. Specifically, Krieg does not teach that the pyrimidine base analoge of cytosine can replace cytosine without impairing immunostimulatory activity of the oligonucleotide and Liu and Wise, given the misrepresentation of the teachings therein by the instant Office Action, fail to provide any information regarding pyrrolo-dC that would be useful in the instantly claimed invention. Thus, the Office Action has failed to make its prima facie case of obviousness. Reconsideration and withdrawal of the rejection are respectfully requested.

Provisional obviousness-type double patenting

Claims 1 and 31 are provisionally rejected over various claims of copending Application Nos. 10/361,111; 10/865,245; 11/153,054; and 11/174,002.

As stated by the Examiner, this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note that, with regards to patent term, U.S. Application Nos. 10/361,111; 10/865,245; 11/153,054; and 11/174,002 are the later filed applications.

Therefore, if this provisional double patenting rejection is the only remaining rejection in the application, Applicants request that the Examiner withdraw the rejection in the instant [earlier filed] application thereby permitting this application to issue without need of a terminal disclaimer. (See MPEP §804(I)(B)). Once the instant claims have been allowed and these rejections have been withdrawn, Applicants will then consider filing a Terminal Disclaimer or take any other action deemed necessary in the later filed, copending applications.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

July 12, 2010

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